## REMARKS

Applicant has amended Claim 1 and canceled Claim 12. Thus, Claims 1-11 and 13-25 are presented for examination. The specific changes to the amended claims are shown above in the Amendments to the Claims, wherein the insertions are underlined and the ~~deletions are stricken through~~. Applicant responds below to rejections made by the Examiner in the Office Action of December 21, 2006.

### I. Election/Restrictions

Applicant elected Group I (Claim 1-25) in the Response to Restriction Requirement filed on May 23, 2006. Applicant has cancelled the claims of Group II (Claims 26-29) without prejudice to their continued prosecution in one or more divisional, continuation, or continuation-in-part applications. Applicant respectfully submits that Claim 1 is generic to the species of Claims 8 and 9, all of which were included in Restriction Group I. Although Claims 8 and 9 recite species of endogenous antibody-cleaving enzymes that were not elected, Applicant respectfully submits that Claims 8 and 9 should be rejoined once the underlying base claim, Claim 1, is deemed allowable.

### II. Rejections under 35 U.S.C. § 112

The Examiner has rejected Claim 1 (and dependent claims 2, and 6-15) under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner states that Claim 1 is indefinite for the recitation of "adjusting the conditions of the cell media" because this limitation has been interpreted to mean "any manipulation to the cell medium," and that it may thus include "adding a new enzyme or any supplement to the medium to activate for example, a preproenzyme." Applicant has amended Claim 1 so that it now recites, *inter alia*, "wherein the adjusted conditions are selected from the group consisting of temperature conditions and pH conditions." The claims depending from Claim 1 thus also contain this limitation. Support for the amendment can be found in the present specification at, for example, paragraphs [0007], [0009], [0013], [0042]-[0044], [0050], and [0065]. Applicant respectfully submits that the amendment clarifies the term "adjusting the conditions of the cell media," and overcomes the rejection.

The Examiner has also rejected Claim 12 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Specifically, the Examiner states that Applicant has not met the burden of establishing public availability of the cell line CHO-DG44, and that a biological deposit of the cell line CHO-DG44 is therefore required. Although Applicant maintains that the cell line CHO-DG44 is well known and publicly available, to advance prosecution, Applicant has canceled Claim 12, and respectfully submits that the rejection is now moot.

The Examiner has also rejected Claims 1-20 and 22-25, as allegedly being indefinite for failing to point out and distinctly claim the subject matter which Applicant regards as the invention.

More specifically, the Examiner states that Claims 1-18 are indefinite for the recitation of "endogenous enzyme" because in Claim 1 it is unclear where an endogenous enzyme is located for targeted activation. As amended, Claim 1 recites, *inter alia*, "at least one endogenous enzyme in said cell media." The claims depending from Claim 1 thus also contain this limitation. Support for the amendment can be found in the present specification at, for example, paragraphs [0009], [0014], and [0065]. Applicant respectfully submits that the amendment clarifies where the endogenous enzyme is located and overcomes the rejection.

Further, the Examiner states that Claims 19, 20, and 22-25 are indefinite for the recitation "activating endogenous aspartyl enzyme activity," alleging that it is unclear what is meant by "activating." Applicant respectfully submits that the present specification discusses enzyme activation extensively, and provides ample guidance on the meaning of the term "activating." For example, one passage states:

> As discussed above, enzymatic digestion of antibodies by activation of an endogenous enzyme such as papain, or a similar enzyme, results in two identical antigen-binding fragments, known also as "Fab" fragments, and a "Fc" fragment, having no antigen-binding activity but having the ability to crystallize. Digestion of antibodies with the endogenous enzyme pepsin, or similar enzymes, results in a "$F(ab')_2$" fragment in which the two arms of the antibody molecule remain linked and comprise two-antigen binding sites. The $F(ab')_2$ fragment has the ability to crosslink antigen and has equivalent binding affinity to intact antibody molecules. Of course, embodiments of the invention are not limited to activation of any particular enzyme. Activation of any endogenous enzyme that cleaves an antibody is within the scope of the present invention.

Specification at page 6, paragraph [0017]. One of ordinary skill would thus understand that aspartyl enzymes (such as pepsin), when activated, cleave whole antibodies to make $F(ab')_2$ fragments. Techniques for activating both cysteinyl proteases and aspartyl proteases, as well as techniques for activating only aspartyl proteases are also discussed in the specification:

> In one embodiment, enzymatic digestion of the secreted antibodies by aspartyl proteases, cysteinyl proteases, or a combination of both types of proteases is initiated by lowering the pH of the cell media to about pH 3.5 and adjusting the temperature to about 37° C. Once the antibodies have been digested by the activated enzymes, further digestion by the enzymes can be inhibited by altering the growth conditions. The particular endogenous enzyme that is activated in the media can be selected by varying the culture conditions. For cysteinyl proteases can be specifically and irreversibly inhibited adding cysteine protease inhibitors such as E-64 (Molecular Probes), or by increasing the pH of the media to 8.5 and incubating the reaction mixture for approximately two hours. Following this inactivation at pH 8.5, the media can be brought to pH 3.5 and 37° C in order to specifically activate any aspartyl proteases in the media. Thus, this embodiment is useful for generating of $F(ab')_2$ fragments since only the aspartyl proteases will act upon the immunoglobulins in the cell media.

*Id.* at pages 4-5, paragraph [0013]. One of ordinary skill in the art would therefore understand "activating endogenous aspartyl enzyme activity" to mean converting an aspartyl enzyme from a state in which it does not cleave antibodies to a state in which it does cleave antibodies. One of ordinary skill would also understand that the techniques described in the specification are exemplary, and not limiting, and that other techniques (such as setting the conditions to other temperature and/or pH levels) could also be used, depending on the enzymes and/or antibodies.

The Examiner has also rejected Claims 1-25 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Specifically, the Examiner states that:

> [T]he specification, while being enabling for a method of generating antibody fragments according to the method steps of clarifying the conditioned media, stabilizing the temperature at 37° C, and adjusting the pH to about 3.5 to activate endogenous enzymes for cleaving Ig molecules, does not reasonably provide enablement for any adjustment to the cell media to activate an endogenous enzyme to specifically cleave an antibody in order to generate antibody binding fragments.

December 21, 2006 Office Action at 8. As discussed previously, Claim 1 has been amended so that it now recites, *inter alia*, "wherein the adjusted conditions are selected from the group consisting of temperature conditions and pH conditions." Applicant notes that techniques in addition to "stabilizing the temperature at 37° C, and adjusting the pH to about 3.5" are also disclosed. For example, experiments were also conducted with pH levels of 5.0, 4.5, 4.0, 3.5, 3.0, and 2.5. *See* Specification at page 15, paragraph [0050]. The notation in paragraph [0051] that "maximal" activity occurred at pH 3.5 should not be read to mean that 3.5 is the only pH that can be used. Simultaneous activation of an aspartyl enzyme and deactivation of a cysteinyl enzyme at pH 8.5 is also disclosed in the present specification. *See* Specification at page 13, paragraph [0043].

One of ordinary skill in the art will, upon reading the present specification, appreciate that not all enzymes are the same, and that reasonable experimentation will allow such a person to determine the optimal conditions for such different enzymes, and thus use the present invention within the scope of the claims.

Accordingly, Applicant respectfully requests withdrawal of the § 112 rejections.

## CONCLUSION

Applicant has endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. Any claim amendments which are not specifically discussed in the above remarks are made in order to improve the clarity of claim language, to correct grammatical mistakes or ambiguities, and to otherwise improve the capacity of the claims to particularly and distinctly point out the invention to those of skill in the art.

In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is respectfully requested. If the Examiner has any questions which may be answered by telephone, the Examiner is invited to call the undersigned directly.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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By: _____

Erik T. Anderson
Registration No. 52,559
Attorney of Record
Customer No. 20,995
(619) 235-8550

3529888
031307